



Chromosomal abnormalities in isolated persistent left superior vena cava: A systematic review and meta-analysis

İzole persistan sol superior vena kavada kromozom anomalileri: Sistematik derleme ve meta-analiz

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Abstract

Persistent left superior vena cava (PLSVC) is the most common systemic venous anomaly detected prenatally, yet the risk of chromosomal abnormalities in truly isolated cases remains uncertain. This systematic review and meta-analysis aimed to determine the pooled rate of chromosomal anomalies in fetuses with isolated PLSVC and no associated structural anomalies, with particular attention to extractable denominators for genetic testing. A systematic search of PubMed/MEDLINE, EMBASE, and the Cochrane Library was performed from January 2000 through March 2026. Studies reporting data on chromosomal anomalies in fetuses with sonographically confirmed, isolated PLSVC were eligible. Isolated PLSVC was defined as bilateral superior vena cava without intracardiac or extracardiac structural anomalies. When a study reported a larger isolated clinical cohort but conducted chromosomal testing only in an extractable subgroup, the genetically assessed isolated subgroup was used as the denominator for the primary chromosomal analysis. Proportions were pooled using the Freeman-Tukey double arcsine transformation and a random-effects DerSimonian-Laird model. Thirteen studies encompassing 699 genetically assessed isolated PLSVC fetuses were included in the quantitative synthesis. Thirteen chromosomal anomalies were identified, yielding a pooled chromosomal anomaly rate of 2.2% (95% confidence interval: 0.9-4.1%) with low heterogeneity ($I^2=29.0\%$, $p=0.15$). Sensitivity analyses demonstrated the robustness of the findings. Although the risk of chromosomal abnormalities in sonographically isolated PLSVC is low, it is not negligible. Therefore, isolated PLSVC should not be considered an indication for routine invasive prenatal diagnosis, and clinical decision-making should be individualized based on maternal age, serum screening or cell-free DNA results, nuchal translucency findings, detailed fetal anatomical assessment, and patient preference.

Keywords: Persistent left superior vena cava, chromosomal anomaly, prenatal diagnosis, meta-analysis, systematic review

Öz

Persistan sol superior vena kava (PLSVC), prenatal dönemde en sık saptanan sistemik venöz anomalilerden biridir ve izole olgularda kromozom anomalisi riski konusunda mevcut veriler sınırlıdır. Bu sistematik derleme ve meta-analizin amacı, izole PLSVC saptanan fetuslarda kromozom anomalisi oranını, özellikle genetik inceleme yapılan olgulara ait doğru payda kullanılarak güncellenmiş ve düzeltilmiş verilerle belirlemek ve prenatal danışmanlık açısından klinik olarak ihtiyatlı bir yorum sunmaktır. PubMed/MEDLINE, EMBASE ve Cochrane Kütüphanesi Ocak 2000-Mart 2026 tarihleri arasında tarandı. İntrakardiyak veya ekstrakardiyak yapısal anomali eşlik etmeyen, ultrasonografik olarak doğrulanmış izole PLSVC olgularında kromozom anomalisi verisi bildiren çalışmalar dahil edildi. İzole PLSVC, intrakardiyak veya ekstrakardiyak yapısal anomali olmaksızın bilateral superior vena kava varlığı olarak tanımlandı. Bir çalışmada klinik olarak izole kohort daha büyük olmasına rağmen kromozom incelemesi yalnızca ayrı bir alt grupta yapılmışsa, primer analizde genetik olarak değerlendirilen izole alt grup payda olarak kullanıldı. Oranlar Freeman-Tukey çift arkisinüs dönüşümü ve rastgele etkiler DerSimonian-Laird modeli ile havuzlandı. Düzeltilmiş kantitatif senteze 13 çalışma ve genetik açıdan değerlendirilmiş 699 izole PLSVC fetusu dahil edildi. Toplam 13 kromozom anomalisi saptandı ve havuzlanmış kromozom anomalisi oranı %2,2 (%95 güven aralığı: %0,9-4,1) olarak bulundu. Heterojenite düşük düzeydeydi ($I^2=29,0$, $p=0,15$) ve bırak-bir-çıkart duyarlılık analizi sonuçların sağlam olduğunu gösterdi. Bulgular, gerçek izole PLSVC'de kromozom anomalisi riskinin düşük ancak sıfır olmadığını göstermektedir. Bu nedenle izole PLSVC tek başına tüm olgularda rutin invaziv tanı endikasyonu

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oluşturmamalı; karar maternal yaş, tarama testleri veya hücresiz DNA sonuçları, ense saydamlığı bulguları, ayrıntılı fetal anatomik değerlendirme ve hasta tercihi dikkate alınarak bireyselleştirilmelidir.

Anahtar Kelimeler: Persistan sol superior vena kava, kromozom anomalisi, prenatal tanı, meta-analiz, sistematik derleme

Introduction

Persistent left superior vena cava (PLSVC) is the most common thoracic systemic venous anomaly and usually results from persistence of the left anterior cardinal vein. In most fetal cases, bilateral superior vena cava are present and the left superior vena cava drains into the right atrium through a dilated coronary sinus⁽¹⁾. PLSVC is estimated to occur in approximately 0.3-0.5% of the general fetal population and has been reported in up to 10% of fetuses with congenital heart disease, underscoring its frequent association with structural cardiac anomalies and the clinical importance of distinguishing isolated from non-isolated cases.

Prenatal detection of PLSVC has increased with the routine use of the three-vessel and tracheal view. The finding appears as an additional vessel located to the left of the pulmonary artery. Once PLSVC is identified, the most important clinical step is to distinguish truly isolated PLSVC from PLSVC associated with intracardiac anomalies, extracardiac anomalies, heterotaxy, aortic arch abnormalities, or absent right superior vena cava⁽²⁾. The need for invasive prenatal genetic testing in cases of isolated PLSVC remains controversial. The influential 2016 meta-analysis by Gustapane et al.⁽³⁾ reported an approximately 7% rate of chromosomal anomalies in isolated PLSVC, but this estimate was largely based on small high-risk referral cohorts. Since then, larger cohorts from low-risk or mixed screening settings have become available. During revision of the current dataset, an important denominator issue was identified: some studies reported all clinically isolated cases, whereas chromosomal testing was performed only in a smaller extractable subgroup. Treating untested clinically isolated cases as genetically normal would artificially lower the pooled rate.

Therefore, the aim of this systematic review and meta-analysis was to estimate the chromosomal anomaly rate associated with isolated PLSVC using extractable genetic-testing denominators, where available, and to provide a clinically cautious interpretation to inform prenatal counseling.

Materials and Methods

Ethical Considerations

This study is a systematic review and meta-analysis of published aggregate data; no primary patient data were collected. Ethics committee approval was not required. The study was conducted in accordance with the ethical standards described in the Declaration of Helsinki (revised 2024). Individual patient informed consent was not applicable.

Protocol and Registration

This systematic review and meta-analysis was conducted according to PRISMA 2020⁽⁴⁾ and MOOSE⁽⁵⁾ recommendations. The protocol was registered in PROSPERO (CRD420261416967). The protocol was prospectively registered under the broader title “Genetic and Perinatal Outcomes of Isolated Persistent Left Superior Vena Cava.” The current analysis focuses on chromosomal anomaly rates in the genetically assessed isolated subgroup; analyses of perinatal outcomes and copy-number variants are planned as separate reports.

Eligibility Criteria

Studies were eligible if they reported fetuses with sonographically confirmed PLSVC and provided extractable data for isolated cases without intracardiac or extracardiac structural anomalies. Studies of a single LSVC with an absent right SVC were excluded because this anomaly represents a distinct anatomical and prognostic entity. Case reports, narrative reviews, conference abstracts without extractable data, and duplicate cohorts were excluded.

Exclusion Criteria

Exclusion criteria were: studies without prenatal PLSVC data; postnatal-only or adult-only studies; case reports; reviews; editorials; letters; conference abstracts; technical imaging studies without eligible outcome data; and studies that did not provide extractable data for isolated PLSVC. Studies were also excluded when the isolated PLSVC subgroup could not be separated from non-isolated cases, when chromosomal or genetic outcomes were not reported for isolated cases, or when the denominator of genetically tested isolated PLSVC fetuses could not be determined. In the case of overlapping cohorts, the most recent, largest, or most complete report was retained.

Search Strategy

A systematic search was performed in PubMed/MEDLINE, EMBASE, and the Cochrane Library from January 2000 to March 2026 using the following search strategy: (“persistent left superior vena cava” OR “PLSVC” OR “bilateral superior vena cava”) AND (“chromosome*” OR “karyotype*” OR “aneuploidy” OR “prenatal”). Reference lists of relevant reviews and included articles were hand-searched.

Data Extraction and Correction Rule

Two reviewers independently extracted study characteristics, study setting, total PLSVC cases, isolated PLSVC cases (including those genetically assessed), chromosomal anomaly events, genetic investigation method, and follow-up. For the

primary analysis, the denominator was predefined as the number of isolated PLSVC fetuses with extractable genetic testing data. When a study reported a larger clinical cohort but provided chromosomal data only for an extractable subset of genetically assessed isolated cases, that subset was used as the denominator.

Chromosomal events occurring only in non-isolated groups were not attributed to the isolated cohort. Copy-number variants detected by chromosomal microarray were counted as chromosomal abnormalities only if classified as pathogenic or likely pathogenic by the original study authors. This definition was applied consistently across all included studies, and variants of uncertain significance were not counted as events.

Statistical Analysis

The primary outcome was the pooled proportion of genetically assessed fetuses with isolated PLSVC who had a chromosomal anomaly. The Freeman-Tukey double arcsine transformation⁽⁶⁾ was used to stabilize variances in the presence of zero-event studies, and a random-effects DerSimonian-Laird model⁽⁷⁾ was applied. Heterogeneity was assessed using Cochran's Q and I^2 statistics. Funnel plot assessment was considered only exploratory and is provided as a supplementary figure because the number of events was insufficient for reliable asymmetry testing. Analyses were performed in Python (statsmodels), and individual-study confidence intervals (CIs) were calculated using Wilson score interval. The Freeman-Tukey transformation was chosen because it remains well-defined for zero-event studies without requiring an arbitrary continuity correction; nonetheless, we note that its back-transformation has recently been questioned for meta-analyses of proportions, and we treat this as a methodological limitation. A prediction interval could not be reliably calculated given the small number of studies, which limits inference about the range of true effects in individual populations.

A leave-one-out sensitivity analysis was pre-specified to evaluate the influence of individual studies on the primary pooled estimate. Each study was sequentially excluded, and the pooled proportion and heterogeneity statistics (I^2 , τ^2 , Cochran Q, p-value) were recalculated for the remaining k-1 studies.

Risk of Bias and Quality Assessment

The methodological quality and risk of bias of the included observational studies were assessed independently by two reviewers using the Joanna Briggs Institute critical appraisal tools for prevalence studies and case series. The assessment focused on the appropriateness of the sampling frame, clarity of inclusion criteria, reliability of prenatal PLSVC diagnosis, definition of isolated PLSVC, completeness of genetic testing or postnatal follow-up, and adequacy of outcome reporting. Disagreements were resolved through discussion and consensus. Studies were not excluded solely on the basis of quality assessment. As the official JBI tools do not specify this 8-item scoring format, it was adapted by the authors (Supplementary Table S1).

Results

Study Selection

The initial search yielded 1,142 records. After the removal of 394 duplicates, 748 records remained. Following title and abstract screening, 135 records were assessed further. Forty-three full-text reports were assessed for eligibility. Thirty studies were excluded after full-text review. Chaoui et al.⁽⁸⁾ and Head et al.⁽⁹⁾ were removed from the quantitative synthesis because they did not provide extractable chromosomal outcome data for an isolated PLSVC subgroup. Durand et al.⁽¹⁰⁾ reported aortic coarctation outcomes without extractable isolated PLSVC chromosomal data; Özşüremeli et al.⁽¹¹⁾ and Esin et al.⁽¹²⁾ did not separately report the number of isolated PLSVC cases that underwent genetic testing. Thirteen studies were included in the quantitative synthesis. The revised PRISMA flow diagram is presented in Figure 1.

Study Characteristics and Corrected Dataset

The corrected dataset included 699 isolated PLSVC fetuses, with 13 chromosomal anomaly events. The principal corrections were applied to denominator definitions: Choi et al.⁽¹³⁾ was corrected from duplicated values of 130/68 to 65 total and 34 isolated cases; Machevin-Surugue et al.⁽¹⁴⁾, Berg et al.⁽²⁾, Barrea et al.⁽¹⁵⁾, and Esmer et al.⁽¹⁶⁾ were corrected to truly isolated

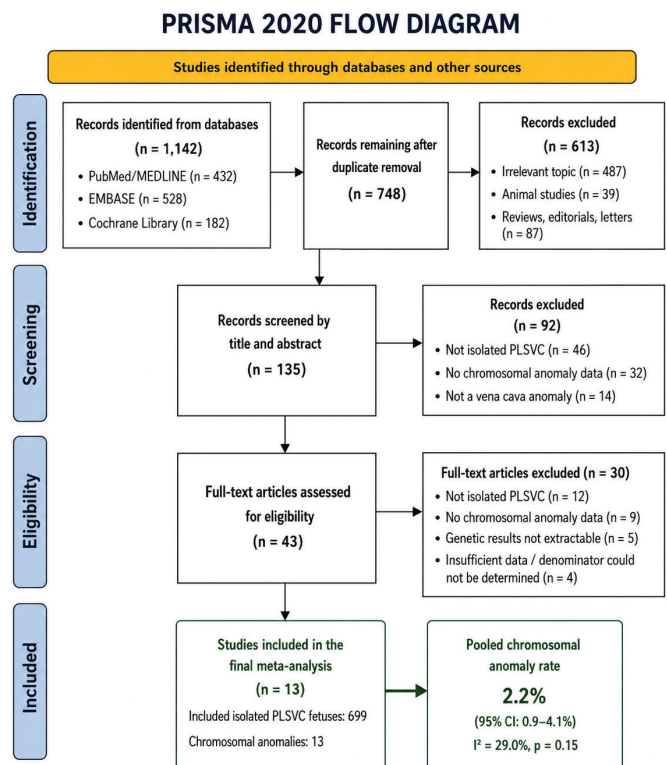


Figure 1. PRISMA 2020 flow diagram illustrating the corrected study selection process

CI: Confidence interval, PLSVC: Persistent left superior vena cava

subgroups rather than broader “no cardiac defect” or abnormal systemic venous return groups; Minsart et al.⁽¹⁷⁾ was corrected to 39 strictly isolated cases with no genetic event. In the 2026 Frontiers in Medicine cohort⁽¹⁸⁾, the primary analysis used 64 genetically tested isolated cases with five anomalies. In the 2023 World Journal of Cardiology cohort⁽¹⁹⁾, 49 isolated cases had no isolated chromosomal anomaly events. Corrected study characteristics are presented in Table 1.

Risk of Bias and Quality Assessment

Of the 13 included studies, 3 were rated as low overall risk of bias [Du et al.⁽²⁰⁾, Choi et al.⁽¹³⁾, Durand et al.⁽²¹⁾], 8 as moderate risk [Berg et al.⁽²⁾, Galindo et al.⁽²²⁾, Barrea et al.⁽¹⁵⁾, Esmer et al.⁽¹⁶⁾, Minsart et al.⁽¹⁷⁾, Yang et al.⁽¹⁹⁾, Li et al.⁽²³⁾, Wei et al.⁽¹⁸⁾], and 2 as high risk [Rein et al.⁽²⁴⁾, Machevin-Surugue et al.⁽¹⁴⁾]. The predominant sources of methodological concern were unclear sampling frames, lack of explicit inclusion criteria for isolated PLSVC, and non-uniform genetic testing protocols. No study was excluded on the basis of quality rating alone. The two high-risk studies contributed small samples (n=9 and n=8, respectively) and exerted minimal influence on the pooled estimate.

Meta-Analysis Results

Across the corrected dataset, 13 chromosomal anomalies were identified among 699 isolated PLSVC fetuses. The pooled chromosomal anomaly rate was 2.2% (95% CI: 0.9-4.1%) using

the Freeman-Tukey transformation⁽⁶⁾ and random-effects DerSimonian-Laird model⁽⁷⁾. Heterogeneity was low ($I^2=29.0\%$, $\tau^2=0.0023$, $p=0.15$). The revised forest plot is shown in Figure 2.

Sensitivity Analysis

Leave-one-out analysis confirmed the robustness of the primary estimate. Pooled rates ranged from 1.4% (95% CI: 0.7-2.5%) when Wei et al.⁽¹⁸⁾ was excluded to 2.7% (95% CI: 1.3-4.5%) when Durand et al.⁽²¹⁾ was excluded. Removal of Wei et al.⁽¹⁸⁾ completely resolved heterogeneity ($I^2=0\%$, $p=0.55$), which is consistent with its large genetically assessed subgroup (n=64, 5 events). Removal of each individual study in turn yielded pooled estimates between 1.4% and 2.7%, with I^2 ranging from 0% to 34.9%, which confirmed that no single study other than Wei et al.⁽¹⁸⁾ materially altered the direction or clinical interpretation of the primary result.

The revised estimate is higher than the preliminary uncorrected estimate of 1.8% because untested, clinically isolated cases were no longer included in the chromosomal denominator. This correction is methodologically important to prevent underestimation of chromosomal risk.

Publication Bias and Small-Study Assessment

A funnel plot was generated as an exploratory assessment (Supplementary Figure S1). This assessment was considered

Table 1. Corrected characteristics and chromosomal anomaly data of included studies

Study	Country	Design	Population	Total PLSVC	Corrected isolated n	Events	Investigation/note
Rein et al. ⁽²⁴⁾	Israel	Retro	Referral	9	9	0	Dilated CS/PLSVC cohort; no isolated chromosomal anomaly
Machevin-Surugue et al. ⁽¹⁴⁾	France	Retro	Referral	22	8	0	Strictly isolated DCS/PLSVC; T21 case excluded (limb anomaly)
Berg et al. ⁽²⁾	Germany	Retro	Referral	82	7	0	Corrected to truly isolated cases
Galindo et al. ⁽²²⁾	Spain	Retro	Referral	54	10	0	Group 1 (no CHD); 0 chromosomal anomalies
Barrea et al. ⁽¹⁵⁾	Belgium	Retro	No CHD ASVR	15	7	1	Bilateral LSVC-to-CS; absent RSVC excluded
Du et al. ⁽²⁰⁾	China	Retro	Routine	181	44	2	Karyotype in isolated PLSVC subgroup
Esmer et al. ⁽¹⁶⁾	Türkiye	Retro	Referral	31	8	0	Corrected to truly isolated subgroup
Choi et al. ⁽¹³⁾	Korea	Retro	Low-risk	65	34	1	Corrected duplicated denominator: 65 total, 34 isolated
Minsart et al. ⁽¹⁷⁾	Canada	Retro	Referral	229	39	0	Strictly isolated PLSVC; no genetic anomaly
Durand et al. ⁽²¹⁾	France	Prosp	Referral	256	113	0	All genetic findings in non-isolated group
Yang et al. ⁽¹⁹⁾	China	Retro	Referral	97	49	0	All abnormal cytogenetics in comorbidity group
Li and Wu ⁽²³⁾	China	Retro	Mixed	425	307	4	Type I PLSVC cohort
Wei et al. ⁽¹⁸⁾	China	Retro	Mixed/ tested	898	64	5	Genetically tested isolated subgroup
Total					699	13	

CA: Chromosomal anomaly, ASVR: Abnormal systemic venous return, CHD: Congenital heart defect, CS: Coronary sinus, DCS: Dilated coronary sinus, PLSVC: Persistent left superior vena cava, Prosp: Prospective, Retro: Retrospective, RSVC: Right superior vena cava

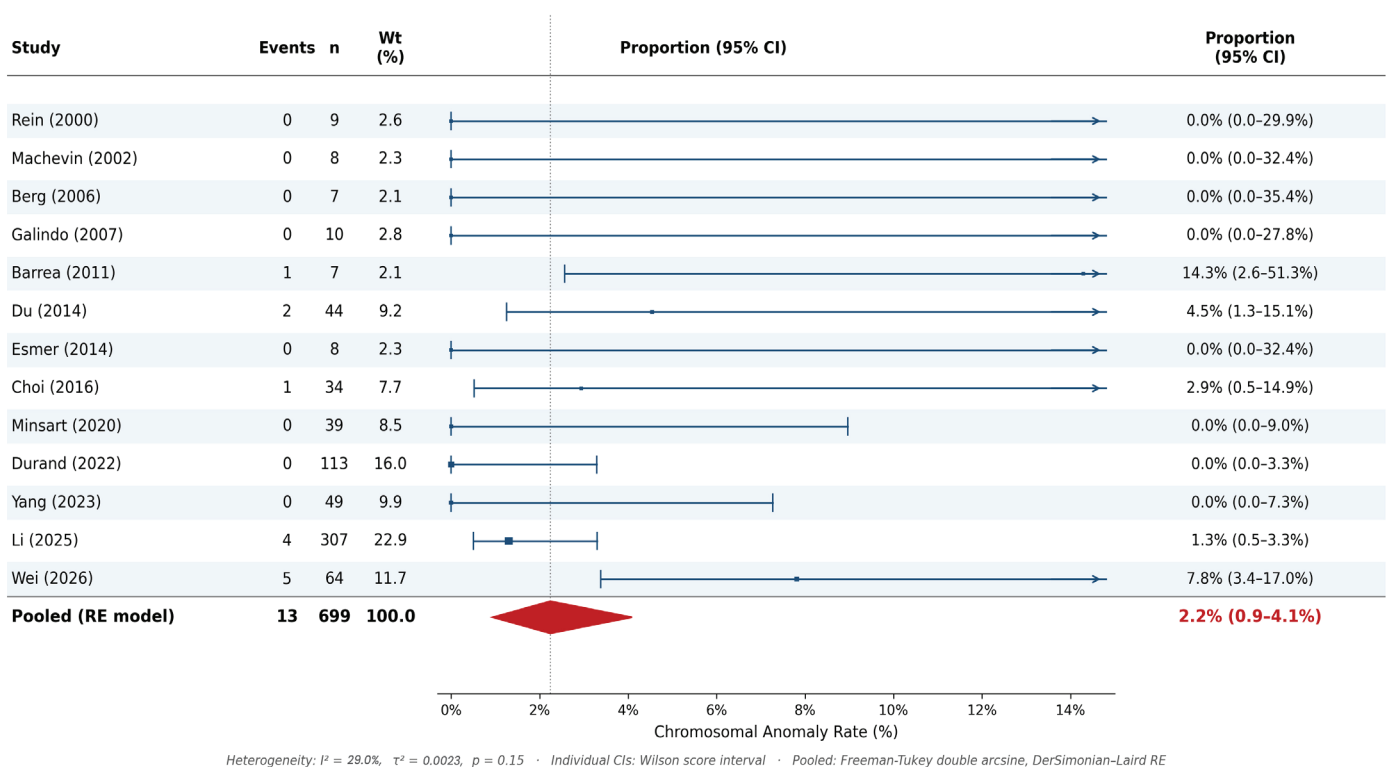


Figure 2. Forest plot of chromosomal anomaly proportions in genetically assessed isolated PLSVC fetuses (Freeman-Tukey double arcsine transformation, DerSimonian-Laird random-effects model)

CI: Confidence interval, PLSVC: Persistent left superior vena cava, RE: Random effects

exploratory because only 13 studies were available and several contained zero events; formal asymmetry testing (e.g., Egger's test) was therefore not emphasized given its limited interpretability in this rare-event meta-analysis of proportions. For the same reason, trimandfill analysis was not performed.

Discussion

This systematic review and meta-analysis estimates the rate of chromosomal anomalies in fetuses with isolated PLSVC as 2.2% (95% CI: 0.9-4.1%). This rate is lower than the 7.0% estimate reported in the 2016 meta-analysis⁽³⁾ and reflects correction of several denominator and isolation-definition errors in the earlier extraction table.

A key methodological lesson of this analysis is that clinical-outcome denominators and genetic-testing denominators are not always identical, as illustrated by the 2026 Frontiers in Medicine cohort⁽¹⁸⁾, in which only 64 of 251 isolated cases underwent genetic assessment; using the smaller genetically tested subgroup as the denominator avoids artificially diluting the chromosomal anomaly rate.

The clinical implications are balanced. Isolated PLSVC should not be treated in the same way as non-isolated PLSVC, which carries a higher risk of genetic and structural abnormalities. However, the corrected rate is not zero. The most defensible

counseling approach involves individualized decision-making that takes into account maternal age, first-trimester screening, cell-free DNA, nuchal translucency measurement, detailed anatomic survey, cardiac assessment, and parental preference. In practice, a normal first-trimester combined screening result or a low-risk cell-free DNA result meaningfully lowers the residual probability of a chromosomal anomaly and may reasonably support a non-invasive approach, whereas an abnormal screening result, an increased nuchal translucency, or any subtle additional finding on detailed fetal echocardiography should prompt reconsideration of invasive testing. When invasive testing is pursued, chromosomal microarray, rather than conventional karyotyping, is the preferred platform because most included studies predate its routine use and submicroscopic abnormalities may otherwise be missed. Ultimately, no single threshold applies uniformly: the counseling discussion should explicitly convey the low but non-negligible background risk identified here, contextualize it alongside the patient's other screening results, and incorporate parental risk tolerance before a shared decision is reached.

Beyond the comparison with Gustapane et al.⁽³⁾, the individual cohorts included here also show variability that merits discussion. Referral-based cohorts with small corrected denominators [e.g., Berg et al.⁽²⁾, Galindo et al.⁽²²⁾, Esmer et

al.⁽¹⁶⁾ reported no chromosomal events, while the two largest genetically assessed subgroups, Li et al.⁽²³⁾ and Wei et al.⁽¹⁸⁾, together contributed 9 of the 13 anomalies observed. This pattern may reflect differences in referral or workup practices, but not necessarily indicate a true difference in underlying risk: centers with larger genetically tested subgroups likely applied more consistent invasive testing protocols, capturing events that smaller or more selective cohorts would have missed. Differences in genetic testing strategy (karyotype alone versus karyotype plus microarray), population source (referral versus routine screening), and regional screening infrastructure likely contribute to the observed heterogeneity across studies and should be considered when extrapolating the pooled estimate to a specific clinical setting.

The distinction between bilateral SVC and single LSVc with absent right SVC remains important. A single LSVc with an absent right SVC is a different entity and was therefore excluded from the present analysis. Likewise, cases with associated intracardiac or extracardiac structural anomalies should not be pooled with truly isolated cases, because doing so inflates risk estimates and may lead to over-counseling.

The strengths of this analysis include a registered protocol, PRISMA-based reporting, strict inclusion criteria, explicit correction of genetic-testing denominators, and a variance-stabilizing transformation suitable for rare-event proportions. Limitations include the retrospective design of many included studies, variable genetic testing strategies, possible selection bias regarding who underwent invasive testing, a small absolute number of events, and the use of aggregate rather than individual-patient data. Because genetic testing was not uniformly performed in all clinically isolated cases, the pooled estimate reflects the chromosomal anomaly rate among genetically assessed isolated PLSVC fetuses rather than the absolute population-level risk. Furthermore, most included studies predate the routine use of chromosomal microarray or copy-number variant sequencing; therefore, the pooled estimate is largely based on conventional karyotyping and may underestimate the true rate of submicroscopic chromosomal abnormalities.

A critical limitation warrants a dedicated discussion. The denominator in each included study consisted exclusively of isolated PLSVC fetuses who underwent invasive genetic testing, not of all isolated PLSVC fetuses identified sonographically. Because invasive testing was typically driven by concurrent risk factors (advanced maternal age, abnormal serum screening, abnormal nuchal translucency, or parental request), the genetically assessed subgroup was systematically enriched for higher-risk pregnancies. This indication bias (workup bias) means that the pooled estimate of 2.2% likely overestimates the true background rate of chromosomal anomalies in unselected, low-risk, isolated PLSVC pregnancies. Prospective cohort

studies that offer standardised genetic evaluation to all isolated PLSVC cases, regardless of concurrent risk factors, are required to establish the true population-level rate.

Conclusion

In fetuses with sonographically isolated PLSVC, the pooled chromosomal anomaly rate is approximately 2.2% (95% CI: 0.9–4.1%). Isolated PLSVC in the absence of additional risk factors, should not routinely trigger invasive prenatal diagnosis; the available evidence does not support invasive testing solely on this basis. A comprehensive risk assessment incorporating maternal age, serum screening or cell-free DNA, nuchal translucency, detailed anatomic evaluation, and patient preference should guide counseling; individualized decision-making remains the most appropriate management strategy. If invasive testing is selected, chromosomal microarray analysis may be considered in accordance with current prenatal genetic practice.

Ethics

Ethics Committee Approval: This study is a systematic review and meta-analysis of published aggregate data. No primary patient data were collected; therefore, ethics committee approval was not required. The study was conducted in accordance with the Declaration of Helsinki (revised 2024).

Informed Consent: Not required.

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Footnotes

Authorship Contributions

Concept: S.S.D., B.D., Design: S.S.D., B.D., Data Collection or Processing: S.S.D., B.D., Analysis or Interpretation: S.S.D., B.D., Literature Search: S.S.D., B.D., Writing: S.S.D., B.D.

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Supplementary Table 1 Link: <https://d2v96fxpocvxx.cloudfront.net/a7b689d1-7b5b-481e-8a29-9bd45e97266c/content-images/5ae59765-2ea7-49f6-88d4-6f43a2b61130.pdf>

Supplementary Figure 1 Link: <https://d2v96fxpocvxx.cloudfront.net/68ab204c-182b-49da-b227-bc7efe058632/content-images/370941aa-d4d1-4d12-bcdc-45b892370aa0.pdf>

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